

# Phenomenological modeling of DNA overstretching

Ray W. Ogden

Department of Mathematics, University of Glasgow,  
Glasgow G12 8QW, Scotland, UK  
e-mail: rwo@maths.gla.ac.uk

Giuseppe Saccomandi

Dipartimento di Ingegneria Industriale,  
Università degli Studi di Perugia, 06125 Perugia, Italy  
giuseppe.saccomandi@mec.dii.unipg.it

Ivonne Sgura

Dipartimento di Matematica,  
Università degli Studi di Lecce, 73100 Lecce, Italy  
e-mail: ivonne.sgura@unile.it

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## Abstract

A phenomenological model based on the three-dimensional theory of nonlinear elasticity is developed to describe the phenomenon of overstretching in the force-extension curve for dsDNA. By using the concept of a material with multiple reference configurations a single formula is obtained to fit the force-extension curve.

**Keywords:** force-extension curve, overstretching, nonlinear elasticity, limiting chain extensibility

**Abbreviations:** dsDNA, double stranded DNA; ssDNA, single stranded DNA; WLC, Worm like chain.

## 1 Introduction

A typical force-extension curve for dsDNA exhibits three *portions* [1, 2, 3]. During the first portion there is an entropic stretching regime (usually modeled by the worm-like chain), followed by a force plateau in the region of 65 piconewtons, while in the last portion there is a sharp transition from the usual B-form to a new overstretched form, usually designated S-DNA. The structure of S-DNA remains the subject of debate but it should not be confused with ssDNA [4, 5].

The biological function of the overstretching DNA transition is complementary to thermal or pH induced denaturation and for this reason there is considerable attention focused on modeling this phenomenon [6], but there appears to be no general agreement about the models that have been proposed in the literature.

In [7] a model based on a force-induced melting of the DNA double helix was proposed. This implies that S-DNA is made up of a mixture of large islands of separated ssDNA and remnant base-paired B-DNA, and molecular extension is a weighted average of its extension in the two possible states. A two-state worm-like chain has been also proposed in [8]. In several papers the idea that the overstretching behavior of DNA may be modeled by a sort of *mixture* theory has been applied in the study of B-DNA to S-DNA transition as a function of solution conditions, including variations in temperature, pH and ionic strength (see, for example, [9]). In [10], by using a thermodynamical model for tension-melted dsDNA it is argued that the overstretching transition cannot be explained in terms of *conversion* of double helix to noninteracting polynucleotide strands. This is because two parallel noninteracting ssDNAs cannot explain quantitatively the mechanical properties of S-DNA. This is argued directly from an examination of the experimental data by the authors [10]. The Rouzina and Bloomfield model [7, 9] is therefore criticized because in the B-ss scenario the overstretched state should be associated with a constant force between the B-DNA and ssDNA lower than that observed.

The aim of the present note is to present a new framework for describing the overstretching phenomena. Our model is developed using a non-standard version of the phenomenological theory of nonlinear elasticity where the stress is determined as a function of the deformation gradient calculated with respect to a *varying reference configuration* in a such a way that it is possible to introduce micro-mechanical considerations. This idea was introduced originally by Eckart [11] and then developed more recently by Rajagopal and Wineman [12, 13] in order to formulate constitutive equations for materials that undergo deformations induced by microstructural changes. Recently De Tommasi et al. [14] have proposed a micro-mechanical interpretation of this theory that may be quite useful in the study of the overstretching phenomenon.

The general form of the constitutive equation for nonlinear elasticity is expressed in terms of a strain-energy function. In the standard theory it is assumed implicitly that the material response is due to a molecular mechanism that does not change during the deformation process under consideration. In single-molecule experiments on DNA, this assumption may be considered valid only on the first portion of the force-extension curve. At a certain moment the hydrogen bonds between strands start to break and there is a fundamental change in the molecular mechanism responsible of the overall material response. In the case of DNA these microstructural changes are driven by several factors: stretching, salinity, temperature, etc. From a micro-mechanical point of view it is possible to look at the nucleotides as particles that are connected by two different types of chains. A fraction of the chains is elastic and endows the DNA molecule with nonzero stiffness. The complementary chains are breakable and are responsible for the alteration of the molecule. The stress in each

breakable chain is zero until a certain activation threshold is reached and after a limiting value of the strain is overcome. We assume that a continuous process of microstructural conversion occurs after the deformation increases beyond a threshold value. In this initial model we shall neglect any factors such as salinity, temperature or ionic strength that are not strictly mechanical. We emphasize that instead of considering the *conversion* of the double helix to two noninteracting polynucleotide strands, we are considering here a process of conversion related to the rupture of stress-bearing bonds. Upon rupture of the bonds a new microstructural arrangement forms with a new unstressed reference configuration. More details of this constitutive model may be found in [14].

Let us consider a deformation  $\mathbf{x} = \mathbf{x}(\mathbf{X}, t)$ , where  $\mathbf{x}$  is the current position of a particle located at  $\mathbf{X}$  in the undeformed configuration at time  $t = 0$ . The deformation gradient is given by  $\mathbf{F}(\mathbf{X}, t) = \partial \mathbf{x} / \partial \mathbf{X}$  and the left Cauchy-Green tensor by  $\mathbf{B} = \mathbf{F}\mathbf{F}^T$ . We assume that there is a range of deformation for which the material behaves like an incompressible, isotropic elastic material, i.e. the Cauchy stress  $\mathbf{T} = -p\mathbf{I} + \mathbf{T}^{(E,1)}$ , where  $-p\mathbf{I}$  is the indeterminate part of the stress due to the constraint of incompressibility ( $\det \mathbf{F} = 1$ ) and the extra stress takes the form

$$\mathbf{T}^{(E,1)} = 2W_1^{(1)}\mathbf{B} - 2W_2^{(1)}\mathbf{B}^{-1}. \quad (1)$$

The strain-energy function  $W^{(1)} = W^{(1)}(I_1, I_2)$  is a function of the principal invariants  $I_1 = \text{tr}(\mathbf{B})$  and  $I_2 = \text{tr}(\mathbf{B}^{-1})$ , where  $W_i^{(1)} = \partial W^{(1)} / \partial I_i$ ,  $i = 1, 2$ . An activation criterion is needed to determine when the microstructural change begins. This is provided by introducing a scalar deformation state parameter  $s$ . Here, we suppose that  $s = s(I_1, I_2)$  depends on the deformation through  $I_1$  and  $I_2$  for consistency with the requirement of isotropy, although more general forms of  $s$  may easily be adopted. For  $s < s_a$ , the threshold value of  $s$ , no conversion has yet occurred, i.e. all the material is in its original form and the stress is given by (1). On the other hand, for a value of the state parameter  $\hat{s}$  beyond  $s_a$  microstructural changes have occurred and the reference configuration has changed. This implies that the stress is now a function of the relative deformation gradient for the material formed at state  $\hat{s}$  given by  $\hat{\mathbf{F}} = \partial \mathbf{x} / \partial \hat{\mathbf{x}}$ , where  $\hat{\mathbf{x}}$  is the position of the particle in the configuration corresponding to deformation state  $\hat{s}$ . In Figure 1 the original reference configuration, the configuration at  $\hat{s}$  and the current configuration are depicted. The associated Cauchy-Green tensor is given by  $\hat{\mathbf{B}} = \hat{\mathbf{F}}\hat{\mathbf{F}}^T$ .

We shall assume that the new material formed at the state  $\hat{s}$  is still elastic, isotropic and incompressible such that the extra Cauchy stress at state  $s$  in this new configuration formed at the deformation state  $\hat{s}$  is given by

$$\mathbf{T}^{(E,2)} = 2W_1^{(2)}\hat{\mathbf{B}} - 2W_2^{(2)}\hat{\mathbf{B}}^{-1}. \quad (2)$$

Here  $W^{(2)} = W^{(2)}(\hat{I}_1, \hat{I}_2)$  is the strain-energy function of the newly formed material, relative to the reference configuration at  $\hat{s}$ . Another important simplifying assumption is that a single function  $W^{(2)}$  governs the strain energy during the continuous microstructural change. The total current stress is taken

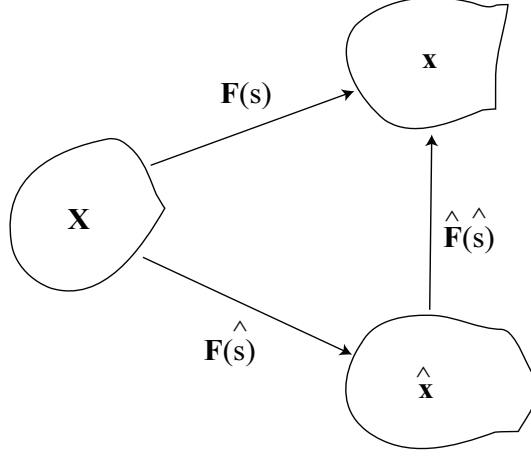


Figure 1: Schematic of a material with an evolving reference configuration

as the superposition of the contributions from the material remaining in its original configuration and from all the new material formed at deformation states  $\hat{s} \in [s_a, s]$ , i.e.

$$\mathbf{T} = -p\mathbf{I} + b(s)\mathbf{T}^{(E,1)} + \int_{s_a}^s a(\hat{s})\mathbf{T}^{(E,2)} d\hat{s}. \quad (3)$$

In (3) the function  $a(s)$  is a conversion rate satisfying  $a(s) = 0$  when  $s \leq s_a$  and  $a(s) > 0$  for  $s > s_a$ , while  $b(s)$  is the volume fraction of the material in the original configuration remaining at state  $s$ , with  $b(s) = 1$  when  $s \leq s_a$  and  $0 \leq b(s) < 1$  for  $s > s_a$ . Thus, to complete the model, constitutive equations for  $W^{(1)}$  and  $W^{(2)}$ , the activation criterion and the conversion rate have to be prescribed. Our model is three-dimensional and fully consistent with the theory of continuum mechanics. To illustrate the ideas quantitatively we begin with a prototype that is empirical and one-dimensional, and we then show how to recast the theory in three-dimensional form.

## 2 The constitutive models

### 2.1 Data sources

We consider the sets of experimental data in [4, 5], which correspond to different salt concentrations. We use measured data  $(x_i, f_i)$ ,  $i = 1, \dots, m$ , here corresponding to a force- ( $f$  in picoNewtons)-extension ( $x$  in microns  $\mu$ ) experiment on a single dsDNA molecule in 250 mM  $[\text{Na}^+]$  buffer solution at 7.5 pH (these data are reported in figure 3 of [4]).

## 2.2 An empirical one-dimensional model

Let  $x$  denote the one-dimensional extension. On the same basis as illustrated above, for the one-dimensional force  $f$  we have

$$f(x) = b(x)f^{(1)} + \int_{x_a}^x a(\hat{x})f^{(2)}(\hat{x})d\hat{x}. \quad (4)$$

In (4) the various quantities  $a(x), b(x), x_a$  have the same meaning as before, with  $x$  replacing  $s$ . Since the process of conversion is continuous we have

$$b(x) = 1 - \int_{x_a}^x a(\hat{x})d\hat{x}, \quad x \geq x_a. \quad (5)$$

The constitutive assumptions we introduce are: for  $f^{(1)}$ , a logistic modification of the original one-dimensional Fung model widely used in biomechanics [15], i.e.

$$f^{(1)}(x) = \frac{\mu_1}{2} \frac{\exp[\beta(x - x_0)]}{\exp[\beta(x - x_0)] + \gamma}, \quad (6)$$

where the material constants  $\mu_1, x_0$  and  $\beta$  have dimensions of force, length and 1/length, respectively, and  $\gamma > 0$  is a dimensionless constant; and, for  $f^{(2)}$ , the WLC interpolation formula

$$f^{(2)}(x) = \mu_2 \left[ \frac{1}{4} (1 - z)^{-2} - \frac{1}{4} + z \right]. \quad (7)$$

Here  $\mu_2 = kT/l_p$ , where  $l_p$  is the persistence length,  $k$  is Boltzmann's constant and  $T$  the temperature (degrees Kelvin),  $z = x/l_c$  and  $l_c$  is the contour length of the molecule. We have chosen a logistic Fung model to capture the first portion of the force-extension curve (i.e. to capture the strain-hardening phenomenon) but without introducing a singularity such as that in the WLC formula. The WLC is used to model the sharp increase in force at the end of the curve just after the plateau. It is clear that the modeling of the plateau zone depends on how the reference configuration evolves, and this may be controlled by the choice of the conversion rate. Usually, in the context of rubber mechanics, very simple models for the conversion function are adopted (for example, quadratic or piecewise linear functional forms). Here we use a functional form suggested by statistical mechanics, namely a probability distribution function computed by considering two possible states for a chain composed of a fixed number of base pairs with a given fixed difference in the energy between the two states. For this purpose let

$$g(x) = \frac{\delta c_1 e^{-c_1(x-c_2)}}{[1 + e^{-c_1(x-c_2)}]^2},$$

where  $c_1, c_2$  and  $\delta$  are constants, and define

$$a(x) = g(x) - g(x_a) \quad x \in [x_a, x_c], \quad (8)$$

with  $a(x) = 0$  otherwise. Here, we are assuming that the conversion has been completed when  $x$  reaches the value  $x_c$ , and this imposes the continuity requirement  $a(x_c) = 0$ , which leads to  $c_2 = (x_a + x_c)/2$ . A plot of the function  $a(x)$  is shown in Figure 2.

We denote by  $C$  the total fraction of the material that can undergo conversion. Then,

$$C = \int_{x_a}^{x_c} a(\hat{x}) d\hat{x}. \quad (9)$$

From the definition of  $C$  in (9), we calculate

$$\delta/C = \frac{[1 + e^{-c_1(x_c - c_2)}][1 + e^{-c_1(x_a - c_2)}]}{e^{-c_1(x_a - c_2)} - e^{-c_1(x_c - c_2)}} - g(x_a)(x_c - x_a).$$

The constitutive parameters to be found in this empirical model are  $\mu_1, \beta, \gamma, \mu_2$  and  $l_c$ . Moreover, we have to fix the activation criterion and therefore we also need values for  $x_a, x_c, c_1$  and  $C$ . At this stage the only *a priori* information about these parameters is that  $C \in [0, 1]$ . The strategy for fitting that we use to deal with the original force-extension data  $(x_i, f_i), i = 1, \dots, m$ , is explained in the Appendix. Since, in principle, several parameters have to be identified in our model, their numerical approximation could pose severe problems (see, e.g., [16]). For this reason we devise a strategy that accounts for the physical interpretation of some of these parameters. A set of parameters identified by the fitting results is given by

$$\left. \begin{aligned} x_a &= 20, & x_c &= 28.754, & C &= 0.50367, \\ \mu_1 &= 64.977, & \beta &= 2.7537, & \gamma &= 0.019288, \\ c_1 &= 0.059145, & \mu_2 &= 25.87, & l_c &= 32.022, \end{aligned} \right\} \quad (10)$$

with residual  $\text{res}^2 = 21.93$ .

In Figure 3 the prediction of the model obtained by using these parameters is shown. The results are quite good, but we believe that better insight might be gained from the three-dimensional model.

### 2.3 Three-dimensional models

In three dimensions the single molecule force-extension experiment is idealized as a simple tension test, for which the deformation is given by

$$x = \frac{1}{\sqrt{\lambda}}X, \quad y = \frac{1}{\sqrt{\lambda}}Y, \quad z = \lambda Z, \quad (11)$$

where  $\lambda$  is the stretch in the axial (i.e.  $z$ ) direction. The current deformation gradient is given in matrix form by  $\mathbf{F}(\lambda) = \text{diag}(1/\sqrt{\lambda}, 1/\sqrt{\lambda}, \lambda)$ , and the corresponding Cauchy-Green deformation matrix is  $\mathbf{B}(\lambda) = \text{diag}(1/\lambda, 1/\lambda, \lambda^2)$ . Hence,

$$I_1 = \lambda^2 + 2\lambda^{-1}, \quad I_2 = \lambda^{-2} + 2\lambda. \quad (12)$$

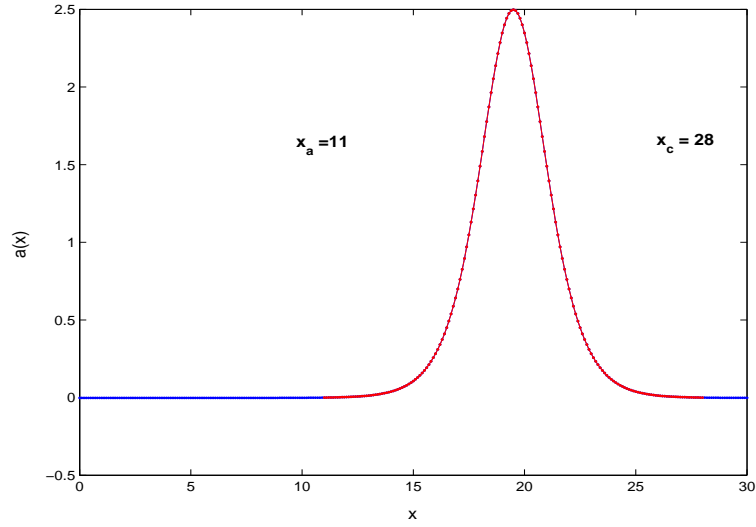


Figure 2: Activation criterion with  $a(x)$  plotted against  $x$ , illustrated for  $x_a = 11$  and  $x_c = 28$  with  $c_1 = 1$ , based on the set of data in Wenner et al. [4] for 250 mM

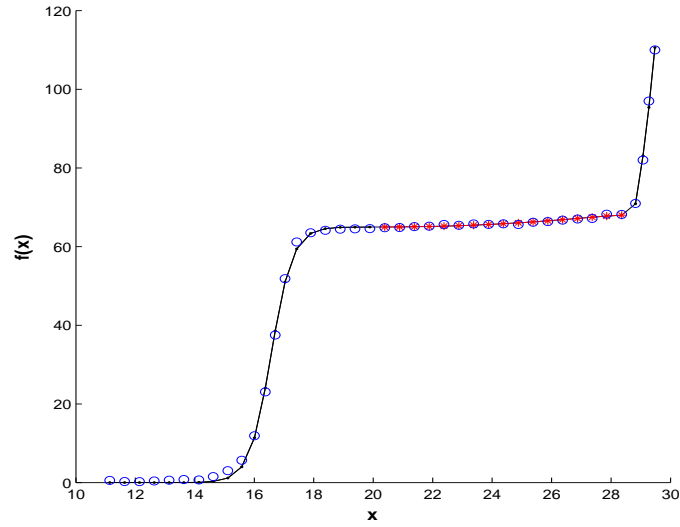


Figure 3: Plot of  $f(x)$  vs.  $x$ . Circles are from the data in Wenner et al. [4] for 250 mM. The curve is obtained from the fitting procedure, which yields the parameter values given in (10) with squared residual  $\text{res}^2 = 21.93$ . The red stars indicate the range of values for which the conversion is active

Since this is a one-parameter deformation, it is possible to establish that there is a one-to-one correspondence between the activation parameter  $s$  and the stretch, and we write  $s = s(\lambda)$ . For this reason we use the terminology *activation stretch*, which we denote by  $\lambda_a$ , instead of a generic activation parameter  $s_a$  (then,  $s_a = s(\lambda_a) = \lambda_a$ ). The deformation gradient at state  $\hat{\lambda}$  is therefore denoted by  $\hat{\mathbf{F}}(\hat{\lambda}) = \mathbf{F}(\lambda)\mathbf{F}^{-1}(\hat{\lambda})$  and we therefore compute

$$\begin{aligned}\hat{\mathbf{F}}(\lambda) &= \text{diag} \left( \sqrt{\hat{\lambda}/\lambda}, \sqrt{\hat{\lambda}/\lambda}, \lambda/\hat{\lambda} \right), \\ \hat{\mathbf{B}}(\lambda) &= \text{diag} \left( \hat{\lambda}/\lambda, \hat{\lambda}/\lambda, \lambda^2/\hat{\lambda}^2 \right).\end{aligned}\tag{13}$$

It follows that, for example,  $\hat{I}_1 = \lambda^2/\hat{\lambda}^2 + 2\hat{\lambda}/\lambda$ . If we consider the class of elastic materials referred to as generalized neo-Hookean materials, with  $W = W(I_1)$ , then from (1) we obtain the principal components of the Cauchy stress tensor in the form

$$t_i = 2\lambda_i^2 W_1 - p, \quad i = 1, 2, 3.\tag{14}$$

The requirement that the lateral surfaces of the specimen undergoing the simple extension are traction free,  $t_1 = t_2 = 0$ , yields

$$p = 2\lambda^{-1}W_1.\tag{15}$$

Generalizing these results to the case (3) the tensile force per unit deformed cross-sectional area necessary to achieve the stretch is given by the Cauchy stress component

$$\begin{aligned}t_3(\lambda) &= 2b(\lambda) (\lambda^2 - \lambda^{-1}) W_1^{(1)} \\ &+ 2 \int_{\lambda_a}^{\lambda} a(\hat{\lambda}) \left( \frac{\lambda^2}{\hat{\lambda}^2} - \frac{\hat{\lambda}}{\lambda} \right) W_1^{(2)}(\hat{\lambda}) d\hat{\lambda},\end{aligned}\tag{16}$$

where

$$b(\lambda) = 1 - \int_{\lambda_a}^{\lambda} a(\hat{\lambda}) d\hat{\lambda}.\tag{17}$$

The corresponding force per unit undeformed area of cross-section is  $\lambda^{-1}t_3(\lambda)$ .

At this point it is necessary to complement (16) with the constitutive equations. We need a constitutive equation for the strain-energy function of the material before the conversion starts, i.e.  $W^{(1)}$ , to model the first portion of the force-extension curve. Then, we also need a constitutive equation for the function  $W^{(2)}$  that governs the mechanical behavior of the newly formed material. This choice is important for modeling the “last” portion of the force-extension curve. The overstretching plateau, as already pointed out, is modeled by the choice of the conversion function  $a(s)$ . For the strain energy  $W^{(1)}$  in the first regime we consider a modification of the strain-energy function, here denoted  $W^F$ , proposed by Fung for modeling biological tissues. This is given by

$$W_1^F = \frac{\mu}{2} \exp[\beta(I_1 - 3)].\tag{18}$$



As for the 1D case, we need to modify this relationship because a saturation phenomenon has to be taken into account. The mechanical behavior characterizing the strain stiffening of the DNA molecule in the first portion of the force-extension curve cannot influence what happens in the plateau zone. For this reason we consider a logistic modification of the (three-dimensional) Fung model (18) analogous to that used for 1D. This is given by

$$W_1^{(1)} = \frac{\mu_1}{2} \frac{\exp[\beta(I_1 - 3)]}{\exp[\beta(I_1 - 3)] + \gamma}, \quad (19)$$

so that

$$W^{(1)} = \frac{\mu_1}{2\beta} \ln(\exp(\beta(I_1 - 3)) + \gamma), \quad (20)$$

which reduces to the neo-Hookean material  $W = \mu_1(I_1 - 3)/2$  when  $\gamma = 0$ . For the strain-energy function  $W^{(2)}$  in the second portion of the deformation range we consider the phenomenological model first proposed by Gent [17] and given by

$$W^{(2)}(\hat{I}_1) = -\frac{\mu_2}{2} J_m \ln \left( 1 - \frac{\hat{I}_1 - 3}{J_m} \right), \quad \hat{I}_1 < J_m + 3, \quad (21)$$

where  $\mu_2$  is the shear modulus for infinitesimal deformations and  $J_m (> 0)$  is the limiting value of  $\hat{I}_1 - 3$  associated with limiting chain extensibility. In the limit as the chain extensibility parameter tends to infinity ( $J_m \rightarrow \infty$ ), (21) also reduces to the classical neo-Hookean model. The model (21) has been discussed in detail by Horgan & Saccomandi [18] and it can be connected with the so-called Freely Jointed Chain (FJC) model. In this case the response function is given by

$$W_1^{(2)} = \frac{\mu_2}{2} \frac{J_m}{J_m - (\hat{I}_1 - 3)}, \quad (22)$$

so that the stress has a singularity as  $\hat{I}_1 \rightarrow J_m + 3$ .

The model we have proposed contains several constitutive parameters that have to be found by using a fitting procedure. The parameters needed to fix the strain-energy functions are  $\mu_1, \beta, \gamma$  and  $\mu_2, J_m$ . Moreover, we use the same activation criterion as was used for the 1D model in (8). Hence, to fix the activation criterion we need to identify the interval with ends  $x_a \rightarrow \lambda_a$  and  $x_c \rightarrow \lambda_c$  and the parameter  $c_1$ . Note that this criterion may easily be reformulated in a way compatible with 3D elasticity in terms of the invariant  $I_1$ . Equation (16) provides a formula for the Cauchy stress, but it is the nominal stress  $\lambda^{-1}t_3(\lambda)$  (force per unit reference cross-sectional area) that is needed for the data fitting. We therefore transform the data set  $(x_i, f_i)$  into the data set  $(\lambda_i, f_i)$ , where  $\lambda_i = 1 + x_i/l_c$ , with the contour length  $l_c$  identified in the 1D case. To match the dimensions of the force  $f$  in the data the stress  $\lambda^{-1}t_3(\lambda)$  has to be multiplied by the reference cross-sectional area, which is unknown. However, this is just a multiplicative factor that is accounted for by incorporating it into the constants  $\mu_1$  and  $\mu_2$ , which then have dimensions of force as in the 1D situation.

The parameters obtained by the strategy explained in the Appendix are

$$\left. \begin{aligned} \lambda_a &= 1.3833, & \lambda_c &= 1.895, & C &= 0.71658, \\ \mu_1 &= 60, & \beta &= 43.772, & \gamma &= 1.193e5, \\ c_1 &= 9.6293, & \mu_2 &= 5, & J_m &= 1.8819, \end{aligned} \right\} \quad (23)$$

with squared residual  $\text{res}^2 = 57.68$ . The result of this fitting is shown in Figure 4.

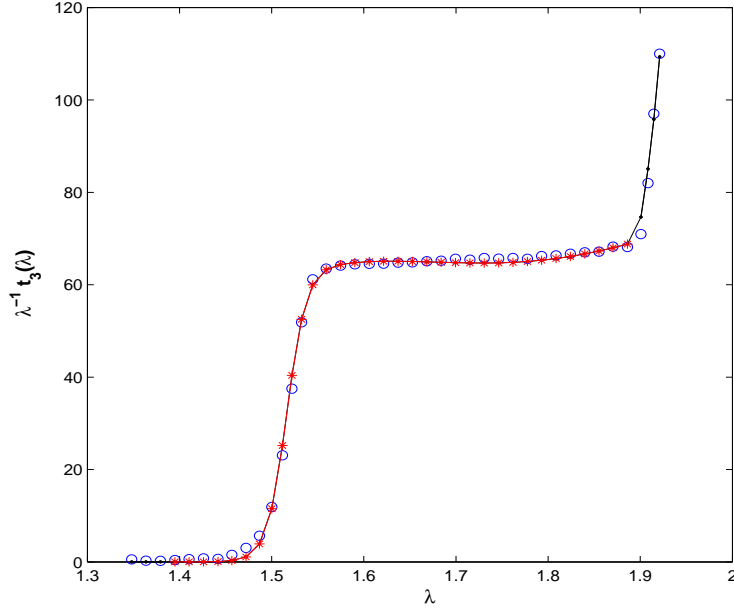


Figure 4: Plot of  $\lambda^{-1}t_3(\lambda)$  vs.  $\lambda$ . Circles are from the data in Wenner et al. [4] for 250 mM. The curve is obtained from the fitting procedure, which yields the parameter values given in (23) with squared residual  $\text{res}^2 = 57.68$ . The red stars indicate the range of values for which the conversion is active. Note that the dimensions of the stress have been converted into ‘force’ by multiplication by the unknown reference cross-sectional area by incorporating this into the parameters  $\mu_1$  and  $\mu_2$

The model proposed herein gives good results in fitting the data, and because it has been formulated within a very general framework it may easily be extended to take into account several variables of biological interest. The model is interesting not only because it comprises a single formula describing the complete force-extension curve, but also from a conceptual point of view. Indeed, as has been argued by Cocco et al. [10], S-DNA cannot be described as

a simple sort of mixture between the dsDNA and ssDNA. The relationship is more complex and it is clarified by the existence of multiple references configurations. We point out that because DNA overwinds when it is stretched, we need a three dimensional model to obtain a complete and realistic picture of the single molecule experiments and our model is just a rigorous version of the toy model proposed by Gore et al. in [19].

### 3 Appendix

The strategy for fitting the theoretical model to the experimental data is based on a nonlinear least squares (LS) approximation as follows. As a first step, we fix *a priori* some parameters from simple biological considerations and we solve the optimization problem for the remaining parameters in order to identify a first optimal subset,  $\mathbf{p}^*$  say. In the successive steps, the strategy consists of implementing the LS algorithm by starting from this solution and then moving in a descent direction by including each time a new free parameter from amongst those that were fixed. The solution found at each step is then used as an initial guess for solving the next LS problem in which a further parameter has to be identified. Only  $x_c$  (for the 1D model) and  $\lambda_c$  (for the 3D model) are always fixed. This assumption implies that in the final part of the experimental curve for  $x > x_c$  (or  $\lambda > \lambda_c$ ) the material is all converted to its new form.

All the computations are performed in Matlab with the *lsqcurvefit* routine (see [20]) for solving nonlinear least squares problems. We allow the algorithm to perform a maximum of 3000 iterations and stop with stringent tolerances on the errors ( $\text{tol} = 1\text{e-}12$ ).

For the 1D model, in the first step we use the optimization procedure to identify the parameters  $\mathbf{p} = [\mu_1, \beta, \gamma]^T$ , while the others are fixed by considering the following physical features:

- the total contour length  $l_c$  is chosen to be slightly larger than the last datum value for the extension since its value locates the asymptote of the WLC;
- $x_0 = x_a$  since the value of  $x_0$  in the logistic function (6) identifies the point where the largest growth occurs, and this corresponds to the meaning of  $x_a$  in the activation criterion;
- since  $\mu_1$  corresponds to the horizontal asymptote of the logistic function, its starting guess is set to almost the force value of the plateau in the data; thus, we set  $\mu_1 = 69$ ;
- we set  $x_a = 20$  so that up to the beginning of the plateau the material is all in its original form. Moreover, we set  $C = 0.5$ , requiring by this assumption a conversion of 50%.

The optimal parameter set identified in this first step, is  $\mathbf{p}^* = [\mu_1^*, \beta^*, \gamma^*]^T = [69.0883, 2.907, 0.0153]^T$ . Hence, by using this first approximation, we define a new sequence of optimization problems, where the fixed parameters are considered free in the (arbitrary) sequence  $[C, \lambda_a, l_c, c_1, \mu_2]$ . The optimal final result is reported in the text and in Figure 3.

The same fitting strategy used for fitting the data with the 1D empirical

model (4) is used for the 3D model (16). For the activation criterion we fix  $\lambda_c = 1.895$ . Moreover, we set  $C = 0.8$ . For the Gent material we fix  $\mu_2$  equal to almost the force corresponding to the plateau, and the parameter  $J_m$ , accounting for the asymptote location, such that  $J_m$  is almost the last numerical value available for the stretch data. At the first stage of the fitting the free parameters are again those of the Fung model and if  $\mathbf{p}^*$  is the set identified in this step, the (arbitrary) sequence in which the other parameters are considered as free is  $[C, J_m, \lambda_a, c_1, \mu_2]$ . In this way a better (lower residual) optimal solution is found and the result is reported in the text and in Figure 4.

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